Navigating the waters of immune checkpoint inhibitor pulmonary toxicity

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ABSTRACT

Background: *The use of immune checkpoint inhibitor (ICI) therapy has improved outcomes for many types of cancer, including primary lung cancer. With increased use of this therapy, immune-related adverse events (IRAE) are identified more frequently and can affect any organ system. ICI-pneumonitis has varied levels of severity at the time of diagnosis that range from mild with nonspecific symptoms to fatal respiratory failure in severe cases. Therefore, early recognition is crucial, and a multidisciplinary approach is recommended for diagnosis, treatment, and surveillance.*

Methods: *We performed a narrative literature review.*

Results: *ICI-pneumonitis is a clinical diagnosis based on medication exposure, clinical symptoms, radiographic abnormalities, and reduced lung function after carefully ruling out other causes, especially infection. Treatment is based on the severity of disease and, in higher-grade cases, consists of holding the ICI and a course of corticosteroids. The duration of treatment depends on the initial response and careful monitoring for recurrence during the corticosteroid taper. Re-challenge of the offending ICI also depends on the initial severity and treatment response and should be considered on a case-by-case basis with a multidisciplinary IRAE team when available. Steroid-sparing agents or prolonged corticosteroid tapers may also be recommended in severe cases. Morbidity and mortality are highest in the acute phase, and survivors after the acute phase often have overall good recovery. Chronic ICI-pneumonitis is rare, with persistent symptoms, lung function decline, and imaging abnormality; management by a pulmonologist is reasonable. Although some risk factors for developing ICI-pneumonitis are noted, there are currently no preventive measures known to limit development of ICI-pneumonitis, and it is still unclear who will develop this IRAE.*

Conclusion: *Increased awareness of ICI-pneumonitis is an important initial step toward more consistent identification and management of this diagnosis. Treatment-related clinical trials and cohort studies are needed to phenotype the disease and advance our understanding and approach.*

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INTRODUCTION

Novel Use of Immunotherapy in Lung Cancer

The landscape of lung cancer management has changed dramatically in recent years. With the growth of smoking cessation programs, screening programs that promote early detection, and a myriad of novel treatment options, lung cancer survival has improved. The 3-year survival has increased from 19% in 2001 to 31% in 2017.[1] In particular, immunotherapy has made a significant impact in outcomes not only for lung cancer but also for melanoma, breast, ovarian, and other cancer types with new indications frequently approved by the U.S. Food and Drug Administration.

Immunotherapy includes a group of medications that target immune checkpoints. Immune checkpoints are a group of cell surface receptors that work to regulate immune response. Normally, this group of receptors works to prevent autoimmunity through regulation of T-cell activity. When these cell interactions are blocked by immune checkpoint inhibitors (ICI), a more robust antitumor immune response is mounted and leads to improved outcomes compared to chemotherapy alone.[2,3] Current U.S. Food and Drug Administration approved

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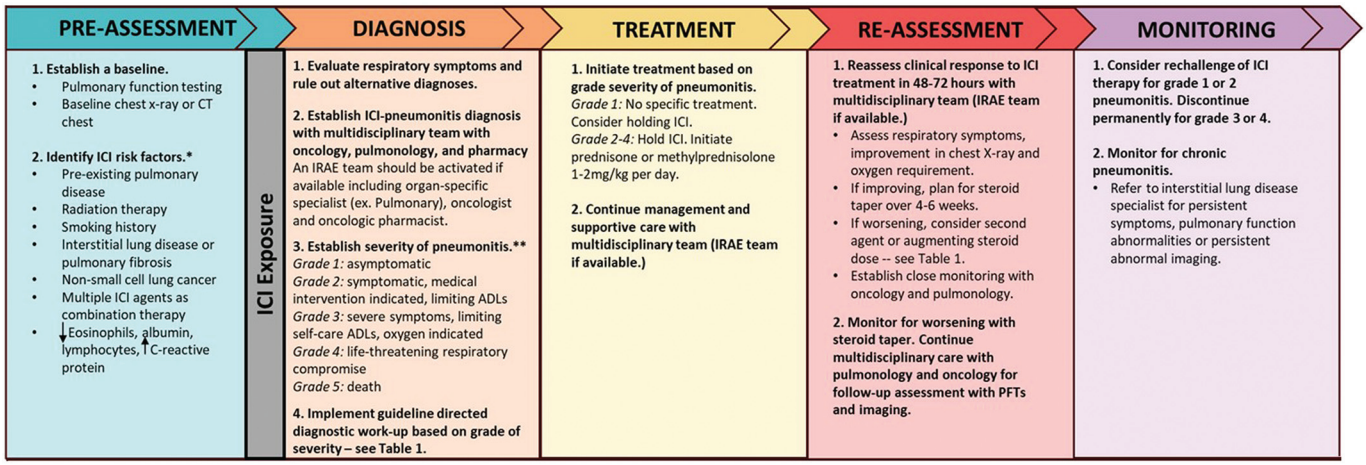
PRE-ASSESSMENT
DIAGNOSIS
TREATMENT
RE-ASSESSMENT
MONITORING
1. Establish a baseline.
• Pulmonary function testing
• Baseline chest x-ray or CT chest
2. Identify ICI risk factors.*
• Pre-existing pulmonary disease
• Radiation therapy
• Smoking history
• Interstitial lung disease or pulmonary fibrosis
• Non-small cell lung cancer
• Multiple ICI agents as combination therapy
• ↓Eosinophils, albumin, lymphocytes, ↑C-reactive protein
ICI Exposure
1. Evaluate respiratory symptoms and rule out alternative diagnoses.
2. Establish ICI-pneumonitis diagnosis with multidisciplinary team with oncology, pulmonology, and pharmacy
An IRAE team should be activated if available including organ-specific specialist (ex. Pulmonary), oncologist and oncologic pharmacist.
3. Establish severity of pneumonitis.**
Grade 1: asymptomatic
Grade 2: symptomatic, medical intervention indicated, limiting ADLs
Grade 3: severe symptoms, limiting self-care ADLs, oxygen indicated
Grade 4: life-threatening respiratory compromise
Grade 5: death
4. Implement guideline directed diagnostic work-up based on grade of severity – see Table 1.
1. Initiate treatment based on grade severity of pneumonitis.
Grade 1: No specific treatment. Consider holding ICI.
Grade 2-4: Hold ICI. Initiate prednisone or methylprednisolone 1-2mg/kg per day.
2. Continue management and supportive care with multidisciplinary team (IRAE team if available.)
1. Reassess clinical response to ICI treatment in 48-72 hours with multidisciplinary team (IRAE team if available.)
• Assess respiratory symptoms, improvement in chest X-ray and oxygen requirement.
• If improving, plan for steroid taper over 4-6 weeks.
• If worsening, consider second agent or augmenting steroid dose -- see Table 1.
• Establish close monitoring with oncology and pulmonology.
2. Monitor for worsening with steroid taper. Continue multidisciplinary care with pulmonology and oncology for follow-up assessment with PFTs and imaging.
1. Consider rechallenge of ICI therapy for grade 1 or 2 pneumonitis. Discontinue permanently for grade 3 or 4.
2. Monitor for chronic pneumonitis.
• Refer to interstitial lung disease specialist for persistent symptoms, pulmonary function abnormalities or persistent abnormal imaging.

Figure 1. *Overview of approach to ICI-pneumonitis. ICI = Immune checkpoint inhibitor; IRAE = immune-related adverse event; ADL = activities of daily living. *From Refs. 6–9. **Adapted from Ref. 26.*

ICIs target cytotoxic T-lymphocyte associated protein 4 (CTLA-4), Programmed death protein 1 (PD-1), and Programmed death ligand-1 (PD-L1).

Immune-Related Adverse Events, Including Pneumonitis

These novel targets and treatment outcomes are encouraging; however, with new treatments come new adverse effect profiles. Although ICIs are highly effective antitumor agents, their use is associated with an increased risk of autoimmune dysfunction, which can result in significant immune-related adverse events (IRAE). IRAEs can involve any organ system, with a wide spectrum of clinical manifestations and severity.

Pulmonary manifestations of IRAEs include pleural effusion, acute eosinophilic pneumonias, sarcoid-like reactions, and pneumonitis. This review focused specifically on pneumonitis, which, although rare, is associated with significant mortality and thus requires early recognition and treatment. The incidence of pneumonitis remains uncertain, with studies that estimate 4–19% in lung cancer patients on immunotherapy.[4] The timeline from drug exposure to onset of symptoms can help guide evaluation because it is usually within the first 3 months of therapy.[5] However, late-onset ICI-pneumonitis cases have been reported several months after cessation of therapy.[5] The pathophysiology of ICI-pneumonitis, similar to other IRAEs, remains poorly understood. The clinical presentation, imaging, and laboratory findings often have overlap with a variety of causes of respiratory failure, which thereby requires clinical suspicion and a diligent effort to rule out other causes, such as infection or heart failure. Given the multiple challenges in diagnosis and poorly understood pathophysiologic mechanism, it is not surprising that ICI-pneumonitis is associated with increased morbidity and mortality.[4] Early recognition and treatment remain crucial but are fraught with significant challenges, and additional studies and research are needed.

METHODS

We performed a narrative literature review by searching PubMed and by using the following search terms: pneumonitis, ICI, immune checkpoint inhibitor, immune related adverse events, IRAE, risk factors, and pulmonary toxicity.

RESULTS

Risk Factors

There are several risk factors for the development of ICI-pneumonitis (Fig. 1). PD-1 inhibition is more associated with development of pneumonitis than PD-L1 inhibition.[6,7] The use of more than one checkpoint inhibitor in combination is also associated with an increased risk of developing pneumonitis.[8] Patients who are treatment naive are also at increased risk.[9] Those patients with non–small cell lung cancer (NSCLC) are more at risk than those with other tumor types, and, within those with NSCLC, squamous cell carcinoma carries the highest risk.[10] Those with adenocarcinoma NSCLC have an increased mortality if ICI-pneumonitis develops. In addition, those with a high tumor burden or those with preexisting pulmonary disease are at elevated risk.[11,12] A history of smoking and exposure to radiation therapy has also been reported to increase risk.[7] On computed tomography (CT) imaging, honeycombing, bronchiectasis, and consolidation were associated with severe pneumonitis development.[13,14] In addition, elevated fibrosis scoring without the usual interstitial pneumonia pattern on imaging is a risk factor for the development of ICI-pneumonitis. Various associations have been suggested between pretreatment laboratory values and the

development of ICI-pneumonitis. Elevated C-reactive protein, lower albumin, and lower eosinophil and lymphocyte count have been associated with ICI-pneumonitis development or severity.[13,14] Studies are incongruent with regard to pulmonary function test (PFT) changes that may be associated with the development or severity of ICI-pneumonitis.[14]

Diagnostic Approach

Establish a Baseline. Before initiating treatment with ICI, physicians should obtain a baseline PFT, including spirometry, lung volumes, and diffusing capacity, and obtain chest imaging to identify and optimize any underlying lung disease that would increase the risk of developing ICI-pneumonitis (Fig. 1).[15–17] These tests are often obtained in patients with lung cancer; however, in patients with nonpulmonary malignancies, this baseline is often not on record.[15–17] A baseline chest radiograph is a minimum recommendation, with far less detail compared with a CT of the chest. A CT of the chest should be performed if the radiograph or PFTs are abnormal. A noncontrasted CT is preferred for evaluation of lung parenchyma; however, testing with contrast for other indications or a positron emission tomography/CT is usually sufficient for baseline testing.

Monitor PFTs and Imaging. When evaluating patients in the outpatient setting, any new respiratory or constitutional symptoms, such as dry cough, fever, chest pain, dyspnea, or generalized fatigue should prompt a consideration for repeated PFTs and CT imaging to assess the change from baseline. A noncontrast or high-resolution CT of the chest is adequate for evaluation unless pulmonary embolism is in the differential diagnosis for new dyspnea in the patient. Society-specific guidelines vary with regard to recommended imaging for various stages of ICI pneumonitis (Table 1).[15,18,19]

Studies[20–22] that looked at PFT changes in ICI-pneumonitis demonstrate a variety of patterns, and there is a paucity of published data. Restrictive changes may develop; reduction in forced vital capacity (FVC) and a concurrent increase in the ratio of forced expiratory volume in 1 second (FEV_1) to FVC (FEV_1/FVC) has been noted in patients who develop ICI-pneumonitis.[20] The development of high-grade pneumonitis is also associated with a reduced diffusing capacity of the lungs for carbon monoxide[21] and total lung capacity.[22] In general, any decline in FEV_1, FVC, or diffusing capacity of the lungs for carbon monoxide should prompt discussion with an IRAE team to determine whether to hold the next dose of ICI and treat with corticosteroids.

In the inpatient setting, PFTs are unlikely to be completed due to patient difficulty in performing and unclear interpretation in the acute setting; however, if available, and can be done, then inpatient PFTs may be helpful. If not able to get PFTs, then a CT of the chest will be the first step in evaluation. Imaging findings in ICI-pneumonitis are variable. Studies report 19–65% patients presenting with organizing pneumonia, 37% with ground-glass opacities, 15–22% with nonspecific interstitial pneumonia, 7–10% with a hypersensitivity pneumonitis pattern, and 10% with acute interstitial pneumonia.[23]

Additional Diagnostic Testing. A crucial step before determining the diagnosis of ICI-pneumonitis is to rule out infection. The symptoms of pneumonitis strongly overlap with infectious symptoms in this immunosuppressed patient population. Respiratory viral panel and sputum cultures should be obtained. If feasible, bronchoscopy with bronchoalveolar lavage (BAL) should also be completed but is more invasive and requires at least moderate sedation. Empiric broad spectrum antibiotics should be started in the interim while awaiting results. Studies have shown that BAL fluid in ICI-pneumonitis will have lymphocytic predominance with < 50% neutrophils and no or low eosinophils; these findings are nonspecific.[24] There have been reports of ICI-related acute eosinophilic pneumonia, which would have elevated BAL fluid eosinophils; however, the clinical course of this variant is not as well studied at this time.[25]

Transbronchial biopsy can be considered; however, this does not typically yield significant results. If a biopsy is done, then typical histologic patterns are cellular interstitial pneumonia, organizing pneumonia, or diffuse alveolar damage.[24] These histopathologic patterns can also be observed in infectious etiologies and thereby require careful clinical correlation. Given these nonspecific findings and procedural risk, which includes pneumothorax, bleeding, or worsening respiratory failure, transbronchial biopsy has largely fallen out of favor clinically when ICI-pneumonitis is the leading diagnostic consideration. Transbronchial biopsy is of value if there is concern for tumor progression or lymphangitic spread of disease, however, is often not a large enough sample to address that question.

Confirming the Diagnosis of ICI-Pneumonitis. ICI-pneumonitis is a clinical diagnosis without definitive biomarkers, laboratory values, pathologic findings, or imaging findings. A thorough evaluation of other etiologies for lung abnormalities and hypoxemia is necessary before treatment of ICI-pneumonitis. Evaluation for heart failure, underlying lung disease, and infection is indicated. Ultimately, the diagnosis requires diligent exclusion of alternative etiologies and clinical correlation of the available data. Multidisciplinary evaluation with a team adjudicating diagnoses is essential in identifying cases and providing consistent management. When building a multidisciplinary team, pulmonary, oncology, and pharmacy personnel should be included.

Table 1 **Comparison of established guidelines for mild, moderate, and severe pneumonitis***

	Grade 1, Mild Pneumonitis			Grade 2, Moderate Pneumonitis			Grade 3 or 4, Severe Pneumonitis		
	NCCN	ASCO	ESMO	NCCN	ASCO	ESMO	NCCN	ASCO	ESMO
ICI therapy	Consider hold	Consider hold	Consider delayed dose	Hold	Hold until improvement to grade 1	Hold	Discontinue	Permanently discontinue	Discontinue
Imaging	Consider CT of the chest with contrast, repeat in 4–6 weeks	Consider chest radiograph or CT with contrast, repeat in 3–4 weeks, sooner if clinical worsening	CT of the chest with contrast, repeat if clinical worsening	CT of the chest with contrast, repeat in 3–4 weeks	N/A	CT of the chest with contrast, weekly chest radiograph	Consider cardiac evaluation	N/A	High-resolution CT of the chest
Bronchoscopy	N/A	N/A	N/A	Consider bronch BAL with or without TBBx	Consider bronch BAL with or without TBBx	Consider bronch BAL	Bronch BAL with or without TBBx	Bronch BAL with or without TBBx	± Bronch BAL
Treatment	No specific treatment; reassess in 1–2 weeks	No specific treatment; if no improvement, then treat as grade 2	No specific treatment; monitor every 2–3 days; if worsening, then treat as grade 2, 3, or 4	Prednisone or IV methylpred 1–2 mg/kg/day	Prednisone 1–2 mg/kg/day, taper over 4–6 weeks	Outpatient daily monitoring; if no evidence of infection and no improvement at 48 hours, then add prednisone 1 mg/kg/day; consider PJP prophylaxis	IV methylpred 1–2 mg/kg/day, assess, taper over 6 weeks; if no improvement at 48 hours, then add infliximab IV 5 mg/kg; a second dose given 14 days later, IVIG, MMF 1–1.5 g b.i.d. with taper	IV methylpred 1–2 mg/kg/day, taper 4–6 weeks; if no improvement at 48 hours, then add infliximab, MMF, IVIG, cyclophos	Methylpred 1–2 mg/kg/day, wean 6–8 weeks; if no improvement at 48 hours, then tocilizumab 8 mg/kg or infliximab 5 mg/kg with or without IVIG; consider MMF or cyclophos

NCCN = National Comprehensive Cancer Network; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; ICI = immune checkpoint inhibitor; CT = computed tomography; N/A = not applicable; bronch BAL = bronchoscopy with bronchoalveolar lavage; TBBx = transbronchial biopsy; IV = intravenous; methylpred = methylprednisolone; PJP = pneumocystis jiroveci pneumonia; IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil; cyclophos = cyclophosphamide; b.i.d. = twice a day.

**Content modified and adapted from NCCN (Ref. 15), ASCO (Ref. 19), and ESMO (Ref. 18) guidelines.*

If available, an IRAE team of subspecialized physicians from each organ system specialty that may be affected by ICI toxicity along with oncology and pharmacy can be activated to assist with diagnosis, treatment, and ongoing surveillance.

Treatment

Initial Treatment Depends on Severity. Treatment for ICI-pneumonitis should be initiated as soon as the initial infectious workup is negative, and pneumonitis remains the leading diagnostic consideration after multidisciplinary evaluation. Pneumonitis severity should be graded based on the Common Terminology Criteria for Adverse Events system.[26] Grading is based on the severity of symptoms and the impact on daily activities. Grades 1 and 2 are mild to moderate in severity and usually treated in the outpatient setting. Grades 3 and 4 are severe and require hospitalization. Grading will determine management based on the guidelines published by the National Comprehensive Cancer Network (NCCN),[15] the American Society of Clinical Oncology (ASCO),[19] and the European Society for Medical Oncology (ESMO).[18] These three sets of guidelines have several nuanced differences in management recommendations, summarized in Table 1.

Systemic Corticosteroids as Initial Management. The backbone of treatment for ICI-pneumonitis is high-dose systemic corticosteroids, and the majority of literature supports 1–2 mg/kg/day as the initial dose. Corticosteroid tapering can be determined based on the underlying lung disease, medical comorbidities, and time to improvement; however, most tapers require 4–6 weeks. If symptoms recur during steroid taper, then the dose should be increased. The taper regimen should be adjusted and may need to be lengthened to ensure adequate control of symptoms and radiographic changes. The term steroid-resistant has been used to describe these cases of initial improvement but worsening with attempts to taper despite a lack of re-challenge of ICI.

Data for pulse dose steroids, described as methylprednisolone 500–1000 mg daily for 3 days, is limited to case reports[15,18,27,28] and some expert opinions.[27] In this realm, the literature proposes the term steroid-refractory ICI-pneumonitis for cases of patients with no initial response to high-dose steroids and suggests that the use of a pulse dose may be considered in these patients. Overall, the data for a pulse dose are more limited and have the risk for harm, especially increased risk of infection.[15,18,28] However, with input from an IRAE or multidisciplinary team, this may be a viable option for patients who are critically ill. Furthermore, pulse dosing is recommended in other IRAEs, such as ICI-encephalitis and ICI-related myasthenia gravis. When patients have improved to grade 1–2, steroid taper may be initiated and completed over 4–6 weeks.[15,18,28]

Steroid Sparing Agents. If a patient does not clinically improve with systemic corticosteroids after 48–72 hours, then additional immunosuppression is recommended for steroid refractory pneumonitis. Intravenous immune globulin (IVIG) is listed in the NCCN,[15] ASCO,[19] and ESMO[18] guidelines for management of steroid refractory ICI-pneumonitis; however, the evidence that specifically supports the use of IVIG in ICI-pneumonitis is not robust and consists of case reports and small case series.[27,29,30] A typical IVIG course is 0.4 × g/kg/day for 5 days, for a total of 2 × g/kg[27] extrapolated from use in myositis-associated interstitial lung disease (ILD). Adverse effects associated with IVIG include anaphylaxis in immunoglobulin A deficiency, acute kidney injury, hemolysis, and venous and arterial thromboembolism.[31,32]

Mycophenolate mofetil, recommended by NCCN,[15] ASCO,[19] and ESMO[18] is also proposed from its use in connective tissue disease–related ILD, has been used to treat steroid refractory ICI-pneumonitis. Adverse reactions associated with mycophenolate mofetil include cytopenia, hepatotoxicity, and increased infectious risk. Because of its slower time to onset of a therapeutic effect (6–12 weeks) compared with other immunosuppressive agents, mycophenolate mofetil is largely considered a better choice for management of chronic ICI-pneumonitis as an outpatient rather than in the acute inpatient setting as a steroid-sparing agent.

Alternatively, infliximab is recommended in all three guidelines[15,18,19] as an additional immunosuppressive agent for treatment of steroid refractory pneumonitis. Unlike IVIG and mycophenolate mofetil, infliximab is less commonly used in treating ILD. It has, however, been used to treat other IRAEs, including colitis and arthritis, and its use in pneumonitis is likely extrapolated from that body of literature and experience.[33] Adverse reactions include new-onset or worsening heart failure, cytopenia, hepatotoxicity, opportunistic pulmonary infections, pneumonitis, and autoimmune antibody development. There are also some reports of potential worse outcomes with infliximab versus IVIG based on case reports.[27,33]

Cyclophosphamide is recommended as an option to treat steroid refractory ICI-pneumonitis in the ASCO[19] and ESMO[18] guidelines. Adverse events include cytopenia, cardiotoxicity, hepatotoxicity, pulmonary toxicity, and hemorrhagic cystitis. There is also risk of second primary malignancy reported with the use of cyclophosphamide.

Tocilizumab is noted in the ESMO[18] guidelines as an option to treat steroid refractory ICI-pneumonitis. A single-center retrospective study that included 12 patients with ICI-pneumonitis observed that 79.4% of

those treated with tocilizumab improved with 1–2 doses.[34] Adverse events associated with tocilizumab include gastrointestinal perforation, anaphylaxis, drug rash with eosinophilia, Stevens-Johnson syndrome, cytopenia, hepatotoxicity, and opportunistic infections.[34] With these various treatment options, the adverse effect profile of each should be considered in light of patient comorbidities before use. Studies are on-going to determine the best treatment for steroid refractory pneumonitis.

Prognosis

The overall prognosis for ICI-pneumonitis varies and is correlated with the initial severity of pneumonitis and the initial response to treatment. The patients' comorbid conditions and functional status must also be considered in prognosticating these cases. The majority of patients with grade 1 or 2 pneumonitis recover but will remain at risk for more severe manifestations and worse outcomes if re-challenge of the checkpoint inhibitor results in higher grades of ICI-pneumonitis.

The prognosis for severe pneumonitis (grade 3 or 4) generally depends on the initial response to treatment. An estimated 10–20% of patients with no initial response to steroids are considered steroid-refractory and may receive higher doses of corticosteroids or initiation of steroid-sparing agents.[27] The patients with steroid-refractory cases have the worst prognosis of ICI-pneumonitis, with an estimated mortality > 60% in most reports.

For severe pneumonitis with the initial response to treatment, the prognosis is better, with most patients significantly improved or resolved after several weeks of therapy. However, ~2% of these patients develop chronic ICI-pneumonitis, which is defined as symptoms that last > 12 weeks, requiring immunosuppressive treatment with steroids with or without an additional immunosuppressive agent.[35] It is likely that the incidence of chronic pneumonitis is underreported but, overall, seems to be low.

The evolution and long-term clinical course of chronic ICI-pneumonitis remains poorly defined. There are reports of organizing pneumonia and fibrotic ILD. A small case series estimates resolution of 50% of the patients in chronic ICI-pneumonitis cases.[35] Patients in chronic ICI-pneumonitis cases should prompt consultation with ILD subspecialists in pulmonology because treatment strategies, including long-term immunosuppressants and antifibrotic therapy, are typically extrapolated from the ILD population and poorly defined in ICI-pneumonitis literature.

SUMMARY

With the growth of immunotherapy for many various types of cancers, the identification of ICI-pneumonitis has become more common and easily enters the differential diagnosis. However, if not steroid responsive, then the treatment options are limited, with significant adverse events associated. At this time, there are no preventive strategies for those at higher risk of ICI-pneumonitis and more work needs to be done in this area. Additional studies are also needed to understand the disease evolution in chronic ICI-pneumonitis and whether antifibrotic agents may play a role in avoiding progressive disease. A step-by-step multidisciplinary approach is recommended for diagnosis, treatment, and surveillance. With more consistent identification of this diagnosis, perhaps treatment-related clinical trials and cohort studies to phenotype the disease will be successful in advancing our understanding and approach.

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